

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

D YOUNG & CO
21 London Road
Southampton, SO15 2AD
ROYAUME-UNI

Date of mailing (day/month/year) 12 February 1999 (12.02.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference FP2149	
International application No. PCT/GB97/02709	International filing date (day/month/year) 08 October 1997 (08.10.97)

1. The following indications appeared on record concerning:

☒ the applicant

 ☐ the inventor

 ☐ the agent

 ☐ the common representative

Name and Address THE UNIVERSITY OF SHEFFIELD Western Bank Sheffield South Yorkshire S10 2TN United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person

 ☒ the name

 ☒ the address

 ☐ the nationality

 ☐ the residence

Name and Address OXFORD BIOMEDICA (UK) LIMITED Medawar Centre Robert Robinson Avenue The Oxford Science Park Oxford, OX4 4GA United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the applicantThe International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Beate Giffo-Schmitt

TENT COOPERATION TRE, Y

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

D YOUNG & CO
21 London Road
Southampton, SO15 2AD
ROYAUME-UNI

Date of mailing (day/month/year) 12 January 1999 (12.01.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference FP2149	
International application No. PCT/GB97/02709	International filing date (day/month/year) 08 October 1997 (08.10.97)

1. The following indications appeared on record concerning:		
<input type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input checked="" type="checkbox"/> the agent
<input type="checkbox"/> the common representative		
Name and Address MARKGRAAF PATENTS LIMITED The Crescent 54 Blossom Street York YO2 2AP United Kingdom	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input checked="" type="checkbox"/> the person	<input type="checkbox"/> the name	<input checked="" type="checkbox"/> the address
<input type="checkbox"/> the nationality		
<input type="checkbox"/> the residence		
Name and Address D YOUNG & CO 21 London Road Southampton, SO15 2AD United Kingdom	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Office concerned	

The International Bureau of WIPO
14, chemin des Colombettes
1211 Geneva 20, Switzerland

Jocelyne Rey Millet

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To

MARKGRAAF PATENTS LIMITED
The Crescent
54 Blossom Street
York YO2 2AP
ROYAUME-UNI

Date of mailing (day month year) 16 April 1998 (16.04.98)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference FP2149	
International application No. PCT/GB97/02709	International filing date (day month year) 08 October 1997 (08.10.97)

1. The following indications appeared on record concerning:			
<input type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input checked="" type="checkbox"/> the agent	<input type="checkbox"/> the common representative
Name and Address WILLIAM JONES (YORK) The Crescent 54 Blossom Street York YO2 2AP United Kingdom		State of Nationality	State of Residence
		Telephone No. 01904 610586	
		Facsimile No. 01904 610909	
		Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:			
<input type="checkbox"/> the person	<input checked="" type="checkbox"/> the name	<input type="checkbox"/> the address	<input type="checkbox"/> the nationality, <input type="checkbox"/> the residence
Name and Address MARKGRAAF PATENTS LIMITED The Crescent 54 Blossom Street York YO2 2AP United Kingdom		State of Nationality	State of Residence
		Telephone No. 01904 610586	
		Facsimile No. 01904 610909	
		Teleprinter No.	
3. Further observations, if necessary:			
4. A copy of this notification has been sent to: <input checked="" type="checkbox"/> the designated Office			

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day.month.year) 22 May 1998 (22.05.98)	
International application No. PCT/GB97/02709	Applicant's or agent's file reference FP2149
International filing date (day month year) 08 October 1997 (08.10.97)	Priority date (day month year) 09 October 1996 (09.10.96)
Applicant LEWIS, Claire, Elizabeth et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

05 May 1998 (05.05.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of the time limit for the priority date in which the election was made, within the time limit under Rule 32.2bis

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Guyne Ray, 11/11/98

PATENT COOPERATION TREATY

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ORDER	
DIARY	
REC D (SOTON)	- 3 FEB 1999
PCT	
FOR	DS CTH

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

D YOUNG & CO
21 London Road
Southampton, SO15 2AD
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

01.02.99

Applicant's or agent's file reference

FP2149

IMPORTANT NOTIFICATION

International application No.

PCT/GB 97/02709

International filing date (day/month/year)

08/10/1997

Priority date (day/month/year)

09/10/1996

Applicant

THE UNIVERSITY OF SHEFFIELD et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1) (see also the reminder sent by the International Bureau with Form PCT/IB 301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

Name and mailing address of the applicant



J. Mounier-Ben Thija

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP2149	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/GB97/02709	International filing date (day/month/year) 08/10/1997	Priority date (day/month/year) 09/10/1996	
International Patent Classification (IPC) or national classification and IPC A61K48/00			
Applicant THE UNIVERSITY OF SHEFFIELD et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

05 05 1998

Name and mailing address: PCT/GBA



Telephone: +44 90 2339 4000
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Telephone: +44 90 2339 4000

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB97/02709

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-44 filed with the demand

Claims, No.:

1-24 filed with the demand

Drawings, sheets:

1-8 filed with the demand

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ *industrial applicability*

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB97/02709

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 15-21 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 11,13-14,17-20,22,24
	No: Claims 1-10,12,16,23
Inventive step (IS)	Yes: Claims 13,20,22
	No: Claims 1-12,14,16-19,23-24
Industrial applicability (IA)	Yes: Claims 1-14,16-19 (YES), 20,22-24 see separate sheet
	No: Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB97/02709

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/02709

1. Reference is made to the following documents :
D1 : WO-A-9521927
D2 : WO-A-9506120
D3 : WO-A-9529704
D4 : Medline Abstract No. XP002056970
D5 : Cancer Research, vol.56 (15 Oct. 1996), pp.4625
D6 : Pathological Society of Great Britain and Ireland, 175th meeting, vol.182 (2-4 July 1997), Abstract No. XP002056969

Regarding point Vi

2. D5 and D6 are cited as intermediary documents. D5 was published after the first priority date but before the two other priority dates claimed by the present application. D6 was published after the three priority dates but before the international filing date. None of these documents was taken into account in the present opinion. However, should the first priority not be valid, D5 could be taken into account for assessing novelty and inventive step in certain countries such as EPC countries. Similarly, should none of the three priorities be valid, D6 could be used for assessing novelty and inventive step.

Regarding point III

3. In claim 15, it is not clear what is meant by "a gene encoding an activating or control product". Claim 14, although very vague, can still be understood in the light of the example of the tetracyclin/promoter of tetracyclin repressor gene system (see page 12 of description). In claim 15, it could be that "the gene encoding an activating or control product" means a gene encoding a cellular factor capable of trans-regulating

including to determine what is meant anyway.

The same comments apply to the expression "an agent for controlling the functional

effectiveness thereof" in claim 21.

As a result, no further opinion will be given concerning these two claims.

Regarding point VIII

4. Claims 12, 15 and 17 are not clear because they show dependence problems. Claim 12 depends from cl. 3-11 and further defines a gene. If cl.3 defines the embodiment wherein the "regulatable agent" comprises a gene, claims 5-11 are not necessarily directed to the embodiment wherein the regulatable agent comprises a gene since the latter claims are dependent from any of the preceding claims, i.e. also depend from cl.1 or 2. Therefore, the subject-matter of claims 5-11 does not necessarily comprise a gene so that claim 12 should not depend from these claims. The same is true from claims 15 and 17, that should only be dependent (directly or indirectly) from claims defining an embodiment wherein the "regulatable agent" comprises a gene.
- 4.1 The application is not concise because claim 5 seems to be redundant. It is not clear that it contains an additional technical feature compared to claim 1.

Regarding point V

5. D1 discloses nucleic acid constructs comprising :
- a) a therapeutic gene, for example a prodrug activation system, linked to
 - b) a hypoxically-inducible expression control sequence (see abstract)
- Examples of a) are thymidine phosphorylase, cytosine deaminase or cytochrome P450 genes. Examples of b) can be found on pages 4-5 and cover some of the promoters exemplified in the present application. The use of such a construct for
- the disclosure discloses cell compositions comprising mononuclear phagocytes and their use in cell therapy (see abstract). Said mononuclear phagocytes contain a recombinant

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/02709

nucleic acid comprising one or several therapeutic genes under the control of regulating promoter elements (claim 1). The therapeutic gene may encode for a tumoricidal/tumor-inhibiting gene (claim 11) and may be used for treating cancer or infections (page 2 l.26-page 3 l.2). Genes can for example encode interferons, TNF, interleukins or antigens of a tumor or of an infectious agent (claim 2). The vector for transforming cells may be an adenoviral vector (claim 6).

D3 discloses a therapeutic composition comprising cells having properties that allow them, when injected to a host, to migrate to specific tissues and to produce an effect against a disease, such as antitumor effect (see abstract). The cells can be genetically altered so as to include a gene enhancing susceptibility to drugs (tk gene...) or a cytokine or lymphokine gene (see page 2 l.29-page 7 l.15). The migrating cells may be monocytes or macrophages (page 19 l.7-15), and the recombinant gene may be inserted in the cells through adenoviral and retroviral vectors (pages 31-34).

5.1 Claim 1 does not appear to be novel over D1, D2 or D3. In D1 for example, the "regulatable agent" would be the therapeutic gene placed under the control of a hypoxically-inducible promoter and the "agent that binds to a mononuclear phagocyte" would be the retroviral vector. As a matter of fact, it is stated on page 14 of the present application that retroviral and adenoviral vectors target mononuclear phagocytes. D2 and D3 would also be novelty-destroying in a similar manner.

5.2 The additional technical features of claims 2-10, 12 and 16 are also disclosed, so that claim 2 would not be novel over D1, claim 3 over D1, D2 and D3, claim 4 over D1, claim 5-8 over D1, D2 and D3, claim 9 over D2 and D3, claim 10 over D1 and D3, claim 12 over D1, claim 16 over D1 and D2.

Since the compositions according to claims 1-10, 12 and 16 do not appear to be novel and since their use for treating cancer or tumors is also disclosed in D1, D2 and D3, the method of claim 23 would not be novel either.

5.3 Although D4 discloses macrophages transfected with a synthetic molecular

... therefore, the subject matter of independent claim 1 would be new.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/02709

- 5.4 Claims 17 and 18 would also be new because the prior art does not disclose a composition according to claim 1 wherein the regulatable gene is placed under the control of a repressor DNA sequence, or wherein a gene capable of killing mononuclear phagocytes is present in addition to the regulatable gene.
- 5.5 No mononuclear phagocytes having internalized (or attached thereto) a hypoxia/stress or ischaemia regulatable agent are explicitly disclosed in the available prior art, so that claims 19 and 20 would appear to be new.
- 5.6 No method of targeting therapeutic agents to hypoxic/ischaemic or stress sites or methods of treatment of conditions associated with hypoxia/stress or ischaemia comprising treating the blood of an individual by transfecting the mononuclear phagocytes was disclosed previously. Claims 22 and 24 would be new.
6. As for dependent claim 11, it does not seem to be inventive. D1, considered as the closest prior art, discloses transformed cells (mainly tumor cells) comprising a therapeutic gene placed under the control of a hypoxia-inducible promoter, said gene being transferred into the cell via plasmid or retroviral vector. Should the person skilled in the art be confronted to the problem of cloning the same nucleic acid construct into a mononuclear phagocyte instead of a tumor cell, this person would combine the teaching of D1 and D4. The latter document clearly discloses that the DNA/mannosylated polylysine system is adequate for transforming macrophages and could be used for cloning therapeutic genes therein.
- 6.1 Dependent claims 14, 17 and 18 do not seem inventive either. If a composition comprises a regulatable agent, for example a gene placed under the control of a regulatable promoter, it seems obvious that the agent capable of inducing or repressing this promoter could be administered in the same composition. As for claims 17 and 18, it is well known in the art of gene therapy to provide additional means of controlling the expression of a therapeutic genes for safety

1033-1034-1035-1036-1037-1038-1039-1040-1041-1042-1043-1044-1045-1046-1047-1048-1049-1050-1051-1052-1053-1054-1055-1056-1057-1058-1059-1060-1061-1062-1063-1064-1065-1066-1067-1068-1069-1070-1071-1072-1073-1074-1075-1076-1077-1078-1079-1080-1081-1082-1083-1084-1085-1086-1087-1088-1089-1090-1091-1092-1093-1094-1095-1096-1097-1098-1099-1100-1101-1102-1103-1104-1105-1106-1107-1108-1109-1110-1111-1112-1113-1114-1115-1116-1117-1118-1119-1120-1121-1122-1123-1124-1125-1126-1127-1128-1129-1130-1131-1132-1133-1134-1135-1136-1137-1138-1139-1140-1141-1142-1143-1144-1145-1146-1147-1148-1149-1150-1151-1152-1153-1154-1155-1156-1157-1158-1159-1160-1161-1162-1163-1164-1165-1166-1167-1168-1169-1170-1171-1172-1173-1174-1175-1176-1177-1178-1179-1180-1181-1182-1183-1184-1185-1186-1187-1188-1189-1190-1191-1192-1193-1194-1195-1196-1197-1198-1199-1200-1201-1202-1203-1204-1205-1206-1207-1208-1209-1210-1211-1212-1213-1214-1215-1216-1217-1218-1219-1220-1221-1222-1223-1224-1225-1226-1227-1228-1229-1230-1231-1232-1233-1234-1235-1236-1237-1238-1239-1240-1241-1242-1243-1244-1245-1246-1247-1248-1249-1250-1251-1252-1253-1254-1255-1256-1257-1258-1259-1260-1261-1262-1263-1264-1265-1266-1267-1268-1269-1270-1271-1272-1273-1274-1275-1276-1277-1278-1279-1280-1281-1282-1283-1284-1285-1286-1287-1288-1289-1290-1291-1292-1293-1294-1295-1296-1297-1298-1299-1300-1301-1302-1303-1304-1305-1306-1307-1308-1309-1310-1311-1312-1313-1314-1315-1316-1317-1318-1319-1320-1321-1322-1323-1324-1325-1326-1327-1328-1329-1330-1331-1332-1333-1334-1335-1336-1337-1338-1339-1340-1341-1342-1343-1344-1345-1346-1347-1348-1349-1350-1351-1352-1353-1354-1355-1356-1357-1358-1359-1360-1361-1362-1363-1364-1365-1366-1367-1368-1369-1370-1371-1372-1373-1374-1375-1376-1377-1378-1379-1380-1381-1382-1383-1384-1385-1386-1387-1388-1389-1390-1391-1392-1393-1394-1395-1396-1397-1398-1399-1400-1401-1402-1403-1404-1405-1406-1407-1408-1409-1410-1411-1412-1413-1414-1415-1416-1417-1418-1419-1420-1421-1422-1423-1424-1425-1426-1427-1428-1429-1430-1431-1432-1433-1434-1435-1436-1437-1438-1439-1440-1441-1442-1443-1444-1445-1446-1447-1448-1449-1450-1451-1452-1453-1454-1455-1456-1457-1458-1459-1460-1461-1462-1463-1464-1465-1466-1467-1468-1469-1470-1471-1472-1473-1474-1475-1476-1477-1478-1479-1480-1481-1482-1483-1484-1485-1486-1487-1488-1489-1490-1491-1492-1493-1494-1495-1496-1497-1498-1499-1500-1501-1502-1503-1504-1505-1506-1507-1508-1509-1510-1511-1512-1513-1514-1515-1516-1517-1518-1519-1520-1521-1522-1523-1524-1525-1526-1527-1528-1529-1530-1531-1532-1533-1534-1535-1536-1537-1538-1539-1540-1541-1542-1543-1544-1545-1546-1547-1548-1549-1550-1551-1552-1553-1554-1555-1556-1557-1558-1559-1560-1561-1562-1563-1564-1565-1566-1567-1568-1569-1570-1571-1572-1573-1574-1575-1576-1577-1578-1579-1580-1581-1582-1583-1584-1585-1586-1587-1588-1589-1590-1591-1592-1593-1594-1595-1596-1597-1598-1599-1600-1601-1602-1603-1604-1605-1606-1607-1608-1609-1610-1611-1612-1613-1614-1615-1616-1617-1618-1619-1620-1621-1622-1623-1624-1625-1626-1627-1628-1629-1630-1631-1632-1633-1634-1635-1636-1637-1638-1639-1640-1641-1642-1643-1644-1645-1646-1647-1648-1649-1650-1651-1652-1653-1654-1655-1656-1657-1658-1659-1660-1661-1662-1663-1664-1665-1666-1667-1668-1669-1670-1671-1672-1673-1674-1675-1676-1677-1678-1679-1680-1681-1682-1683-1684-1685-1686-1687-1688-1689-1690-1691-1692-1693-1694-1695-1696-1697-1698-1699-1700-1701-1702-1703-1704-1705-1706-1707-1708-1709-1710-1711-1712-1713-1714-1715-1716-1717-1718-1719-1720-1721-1722-1723-1724-1725-1726-1727-1728-1729-1730-1731-1732-1733-1734-1735-1736-1737-1738-1739-1740-1741-1742-1743-1744-1745-1746-1747-1748-1749-1750-1751-1752-1753-1754-1755-1756-1757-1758-1759-1760-1761-1762-1763-1764-1765-1766-1767-1768-1769-1770-1771-1772-1773-1774-1775-1776-1777-1778-1779-1780-1781-1782-1783-1784-1785-1786-1787-1788-1789-1790-1791-1792-1793-1794-1795-1796-1797-1798-1799-1800-1801-1802-1803-1804-1805-1806-1807-1808-1809-1810-1811-1812-1813-1814-1815-1816-1817-1818-1819-1820-1821-1822-1823-1824-1825-1826-1827-1828-1829-1830-1831-1832-1833-1834-1835-1836-1837-1838-1839-1840-1841-1842-1843-1844-1845-1846-1847-1848-1849-1850-1851-1852-1853-1854-1855-1856-1857-1858-1859-1860-1861-1862-1863-1864-1865-1866-1867-1868-1869-1870-1871-1872-1873-1874-1875-1876-1877-1878-1879-1880-1881-1882-1883-1884-1885-1886-1887-1888-1889-1890-1891-1892-1893-1894-1895-1896-1897-1898-1899-1900-1901-1902-1903-1904-1905-1906-1907-1908-1909-1910-1911-1912-1913-1914-1915-1916-1917-1918-1919-1920-1921-1922-1923-1924-1925-1926-1927-1928-1929-1930-1931-1932-1933-1934-1935-1936-1937-1938-1939-1940-1941-1942-1943-1944-1945-1946-1947-1948-1949-1950-1951-1952-1953-1954-1955-1956-1957-1958-1959-1960-1961-1962-1963-1964-1965-1966-1967-1968-1969-1970-1971-1972-1973-1974-1975-1976-1977-1978-1979-1980-1981-1982-1983-1984-1985-1986-1987-1988-1989-1990-1991-1992-1993-1994-1995-1996-1997-1998-1999-2000-2001-2002-2003-2004-2005-2006-2007-2008-2009-2010-2011-2012-2013-2014-2015-2016-2017-2018-2019-2020-2021-2022-2023-2024-2025-2026-2027-2028-2029-2030-2031-2032-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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/02709

- 6.2 It is already known from D2 to use recombinant mononuclear phagocytes expressing various tumor-killing or tumor-inhibiting factors for treating cancer, even if it is not expressly stated that mononuclear phagocytes are especially efficient in targeting tumors. D1 describes the use of recombinant cells expressing therapeutic genes controlled by hypoxia-inducible promoters for treating cancer. Therefore, it seems obvious for the person skilled in the art confronted to the problem of providing an alternative therapy for cancer try to use recombinant mononuclear phagocytes expressing a hypoxia-inducible gene, especially since it is known in the art that many tumors contain hypoxic tissue. Therefore, claim 19 does not seem inventive.
- 6.3 However, it was known or suggested previously that mononuclear phagocytes could be especially efficient at targeting therapeutic agents to hypoxic/ischaemic or stress sites, so that claim 22 would be inventive.
Similarly, dependent claim 13 would appear to be inventive, because it is not obvious to combine the above-mentioned cells with a bioreductively activated prodrug.
For the same reason, claim 24 could be inventive too if cancer and tumors were disclaimed. The use of mononuclear phagocytes expressing a hypoxia-inducible gene for treating cancer/tumors seems obvious as already explained in point 6.2 above.

Regarding point VII

7. There are typing mistakes in claims 4 (ischaemica) and 17 (represser).